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OBSTETRICS

Evaluation of 1025 fetal deaths: proposed diagnostic workup

Fleurisca J. Korteweg, MD, PhD; Jan Jaap H. M. Erwich, MD, PhD; Albertus Timmer, MD, PhD; Jan van der Meer, MD, PhD; Joke M. Ravisé; Nic J. G. M. Veeger, PhD; Jozien P. Holm, MD, PhD

OBJECTIVE: We sought to evaluate the contribution of different diagnostic tests for determining cause of fetal death. Our goal was to propose a workup guideline.

STUDY DESIGN: In a multicenter prospective cohort study from 2002 through 2008, for 1025 couples with fetal death ≥20 weeks' gestation, an extensive nonselective diagnostic workup was performed. A panel classified cause and determined contribution of diagnostics for allocating cause.

RESULTS: A Kleihauer-Betke, autopsy, placental examination, and cytogenetic analysis were abnormal in 11.9% (95% confidence interval [CI], 9.8–14.2), 51.5% (95% CI, 47.4–55.2), 89.2% (95% CI, 87.2–91.1), and 11.9% (95% CI, 8.7–15.7), respectively. The most valuable tests for determination of cause were placental examination (95.7%; 95% CI, 94.2–96.8), autopsy (72.6%; 95% CI, 69.2–75.9), and cytogenetic analysis (29.0%; 95% CI, 24.4–34.0).

CONCLUSION: Autopsy, placental examination, cytogenetic analysis, and testing for fetal maternal hemorrhage are basic tests for workup after fetal death. Based on the results of these tests or on specific clinical characteristics, further sequential testing is indicated.

Key words: antepartum stillbirth, cause of death, intrauterine fetal death, workup

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Fetal death is a devastating experience for parents and caregivers. A complex chain of events often precedes the fetal death. Health care workers are responsible for providing support to families and for investigating the cause of death. This information can give insight into why death occurred, which will aid parents in the mourning process. Furthermore, it will be of value in determining recurrence risk, counseling and prevention for future pregnancies, and audit of the care provided, and it enables comparison of health care.[1]

★ EDITORS' CHOICE ★

Unfortunately the cause of death is reported as unexplained in up to two thirds of stillbirths.[2,3] Using a systematic and well-defined approach to evaluate the cause of death reduces this percentage.[4] However, the optimal workup after fetal death has not yet been established and local protocols differ and are often extensive. Consequently, there is a debate on which tests and examinations should be included in an investigative workup to ensure an acceptable chance of determination of the cause of fetal death.

Several reviews on the workup after fetal death have been published,[3,5,6] however a prospective, systematic evaluation of a large cohort of fetal deaths has not yet been performed. Therefore we prospectively analyzed all diagnostic tests of an extensive protocol in which the contribution of each test was evaluated for determining the cause of fetal death according to the Tulip classification.[7] Our goal was to propose a guideline for an optimal workup after fetal death in terms of a high percentage of explained fetal deaths in combination with a minimum of testing.

Materials and Methods

In 2002, we initiated the prospective intrauterine fetal death (IUFD) cohort study in 50 Dutch secondary and tertiary referral hospitals. Inclusion criteria were singleton IUFD diagnosed antepartum ≥20 weeks' gestation. Pregnancy terminations and intrapartum deaths were excluded. The study was approved by the review boards of all hospitals and informed consent was obtained from all participants.

Diagnostic protocol

Data included medical and obstetric history and details on pregnancy and deliv-

From the Departments of Obstetrics and Gynecology (Drs Korteweg, Erwich, and Holm and Ms Ravisé) and Pathology and Medical Biology (Dr Timmer); the Division of Hemostasis, Thrombosis, and Rheology, Department of Hematology (Dr van der Meer); and the Department of Epidemiology, Trial Coordination Centre (Dr Veeger), University Medical Centre Groningen, University of Groningen, Groningen, The Netherlands.

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ery. Before the study started we examined local protocols of participating hospitals regarding diagnostics after IUFD. Subsequently the study protocol was based on these local protocols. Diagnostic tests were included in the study protocol if 70% of hospitals performed these tests after IUFD. For the study all participating hospitals followed the study protocol (Figure 1) and these tests were offered to all women with an IUFD so that each couple with IUFD was managed the same way.

Maternal and fetal blood test results were compared to local laboratory reference values and if greater, were considered abnormal. Maternal and fetal viral serology and microbiological cultures were positive if respectively immunoglobulin levels or culture colonies exceeded the reference values in the local laboratory.

Maternal plasma levels collected on induction of labor of antithrombin, protein C activity, total and free protein S antigen, and Von Willebrand factor (VWF) were measured and the thrombophilias factor V Leiden, prothrombin G20210A mutation (PTG20210A), and lupus anticoagulant were determined in the central laboratory.[8] Presence of maternal anticardiolipin antibodies and a random maternal plasma homocysteine (abnormal >18.5 μmol/L)[9] were tested in local laboratories.

Autopsy and placental examination were performed by surgical and perinatal pathologists in participating hospitals. We urged pathologists to follow the pathology study protocol based on the guidelines of the Royal College of Obstetricians and Gynecologists, the Royal College of Pathologists, and the College of American Pathologists.[7] Cytogenetic evaluation was performed in genetic centers[10] and radiography and magnetic resonance imaging (MRI) by local radiologists.

Adjudication of cause of death

After individual classification of the cause, mechanism, origin of mechanism, and determination of contributing factors of fetal death according to the Tulip classification[7] by an experienced multidisciplinary panel (consisting of 2 obstetricians, an obstetric resident, a perinatal pathologist and, if needed, expertise by a neonatologist, geneticist, or microbiologist), consensus was reached after discussion. The cause was defined as the initial, demonstrable pathophysiological entity initiating the chain of events that had irreversibly led to death. Contributing factors such as smoking and obesity were also identified. In addition, comorbidity was noted such as: hypertension-related disease during pregnancy including chronic hypertension, pregnancy-induced hypertension, preeclampsia, HELLP syndrome, and superimposed conditions.[11] Diabetes-related disease during pregnancy included types 1 and 2 diabetes mellitus and gestational diabetes with or without medication.[12]

Value of diagnostics

Contribution of each diagnostic test for determination of cause of death according to the Tulip classification was evaluated by the same multidisciplinary panel first individually and secondly during the panel sessions. Diagnostics were adjudicated valuable if "establishing cause of death" (an abnormal result of a diagnostic test established a cause) or "excluding cause of death" (a result excluded a cause of death when there was a suspected cause of death based on clinical findings or review of the medical history, current pregnancy, or antenatal investigations). We also registered if a test was "missing for determination of cause of death" (if there was a suspected cause, the test exploring that cause was missing).

Statistics

Categorical variables were expressed as counts and percentages, and continuous data as means with SD or median and ranges, with exact 95% confidence intervals (CIs) given when appropriate. Differences between groups were evaluated by the Fisher exact test or χ^2 test for categorical data. A 2-tailed P value $< .05$ was considered to indicate statistical significance. Statistical analyses were performed using software (SAS, version 9.1; SAS Institute Inc, Cary, NC).

RESULTS

From 2002 through 2008 a total of 1164 couples and their fetal deaths were included, of which 1025 were studied (Figure 1). Investigation into inclusion rates by comparison of death registration yearbooks from participating hospitals yielded an average inclusion of 75% of all IUFDs eligible for the study. Reasons for not including IUFDs were: denied informed consent, a language barrier, logistic problems, and the doctor's reluctance to include women because of an already "known" cause of IUFD at birth. This involved deaths with placental abruption, known chromosomal abnormalities, and major congenital anomalies, which resulted in an underrepresentation of such deaths in our cohort.

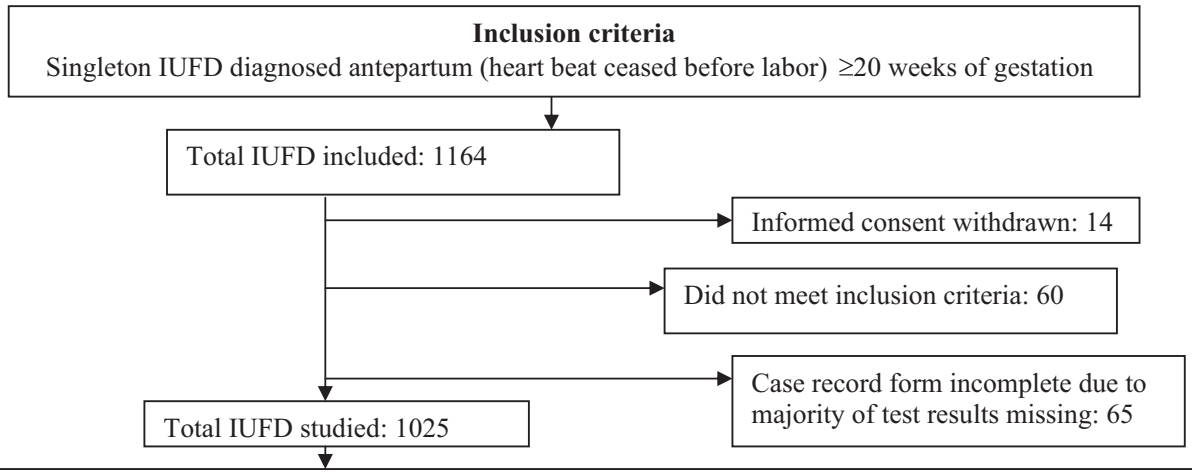
Median age of mothers was 30 years (range, 17–51 years) and median gestational age at determination of IUFD was 32 weeks and 0 days (range, 20 weeks and 0 days–42 weeks and 4 days). The distribution of maternal ethnic origin was 87.1% Caucasian, 4.6% African, 3.8% Eastern, and 4.5% other. Of these mothers 52.7% were nulliparous. Median fetal weight was 1528 g (range, 12–5410 g). Of these babies 37.2% were small for gestational age (<10th growth percentile) and 10.1% large for gestational age (>90th growth percentile) according to Dutch Kloosterman[13] growth charts.

Diagnostic protocol

How often a test of the study protocol was performed varied from 98.7% for placental examination to 3.2% for expert external fetal examination (Figure 1). The results of various abnormal maternal blood tests and the number of women tested are presented in Table 1. Of the women with increased glycated hemoglobin (HbA1c) (7.9%), 61.8% were not known to have diabetes-related disease. Macrosomia and obesity, known risk factors for diabetes,[14] were more prevalent in this group compared to the group with normal HbA1c. Fetal blood tests derived from the umbilical cord were only performed in 10.5% mainly due to the impossibility of drawing (enough) blood after birth.

We recently published on the contribution of coagulation tests.[8] As shown in Table 1, in women with IUFD we more often observed decreased plasma levels of antithrombin (17.1%) and protein C

FIGURE 1
Enrollment of couples with IUFD and diagnostics performed after fetal death



How often a diagnostic test was performed in 1025 fetal deaths
Prior to delivery after determination of IUFD

Mother

- Blood tests: 67.6-98.6% of individual tests performed
  Blood type, Rhesus factor, Thrombocytes, Uric Acid, Urea, Creatinine, Aspartate, Alanine, Lactate dehydrogenase (LDH), Bilirubin, Gamma-glutamyltransferase, C-reactive protein, Thyroid-Stimulating Hormone, Free thyroxine (T4), random plasma glucose, glycated hemoglobin (HbA1c), Kleihauer-Betke, Hemoglobin electrophoresis, Anti-nuclear Antibodies, Antibody screening, HIV, random Homocysteine, Anticardiolipin antibodies
- Viral serology: 79.1-94.0% of individual tests performed
  Toxoplasmosis, Rubella, Cytomegalovirus, Herpes simplex virus, Parvovirus B19, Syphilis, Hepatitis B-surface-antigen
- Coagulation tests: 81.4-93.7% of individual tests performed
  plasma levels of Antithrombin, Protein C, total and free Protein S, von Willebrand factor; inherited thrombophilias Factor V Leiden, Prothrombin G20210A mutation and lupus anticoagulant
- Vaginal-rectal swab: 83.2%

Fetus

- Cytogenetic analysis; amniocentesis or chorionic villus biopsy: 26.2%

After delivery

Fetus

- Blood tests from umbilical cord: 10.5%
  Blood type, Rhesus factor, Hemoglobin, LDH, Bilirubin, Reticulocytes, Creatine phosphokinase
- Viral serology: 3.6-4.5% of individual testsperformed
  Toxoplasmosis, Rubella, Cytomegalovirus, Herpes simplex virus, Parvovirus B19, Syphilis
- Ear throat swab: 72.1%
- Autopsy: 68.8%, external fetal examination by expert if no consent for autopsy: 3.2%
- Cytogenetic analysis: 42.1%; tissue testing of the fetus (fetal blood, fascia lata, pericard, cartilage, or skin), umbilical cord or placenta
- MRI: 6.0%
- Radiography: 39.9%

Placenta

- Placental swab between the membranes: 59.7%
- Pathological examination including histopathology: 98.7%

IUFD, intrauterine fetal death.

Korteweg. Fetal death workup. Am J Obstet Gynecol 2012.

TABLE 1
Abnormal blood tests in 1025 intrauterine fetal deaths

Maternal blood tests % abnormal (n tested)	95% CI	Thrombophilic defects % abnormal (n tested)	95% CI	Prevalence normal population
Thrombocytes <100 x $10^3/\mu$L	3.1 (1011) 2.1–4.3	Acquired thrombophilias		
Uric Acid >0.40 mmol/L	10.6 (956) 8.7–12.7	Antithrombin	17.1 (952) 14.7–19.7	
Urea >7.5 mmol/L	1.6 (976) 0.9–2.7	Protein C	4.2 (834) 2.9–5.8	
Creatinine >100 umol/L	2.4 (1007) 1.5–3.5	Total protein S	2.9 (960) 2.0–4.2	
Aspartate >40 IU/L	8.6 (1001) 6.9–10.5	Free protein S[a]	1.0 (952) 0.4–1.8	
Alanine >40 IU/L	7.6 (1006) 6.0–9.4	VWF	14.3 (954) 12.1–16.6	
Lactate dehydrogenase >250 IU/L	80.6 (988) 78.0–83.0	Inherited thrombophilias		
Bilirubin >26 umol/L	1.7 (928) 1.0–2.8	Factor V Leiden	5.8 (935) 4.4–7.5	5%
Gamma-glutamyl transferase >40 IU/L	6.5 (914) 5.0–8.3	Heterozygous	5.6	
C-reactive protein >10 mg/L	51.3 (832) 47.9–54.8	Homozygous	0.2	
TSH <0.4 mE/L	1.6 (936) 0.9–2.6	Prothrombin G20210A	2.4 (937) 1.5–3.5	3%
TSH >4.0 mE/L	8.9 (936) 7.1–10.9	Heterozygous	2.4	
Free thyroxine <10.0 pmol/L	13.2 (902) 11.1–15.6	Homozygous	—	
Free thyroxine >24.0 pmol/L	0.2 (902) 0.03–0.8	Lupus anticoagulant	1.5 (865) 0.8–2.6	3%
Random plasma glucose 6.1–11.0 mmol/L	19.8 (881) 17.2–22.5	Random homocysteine	2.9 (733) 1.8–4.4	5%
Random plasma glucose ≥11.1 mmol/L	0.9 (881) 0.4–1.8	AC antibodies	5.6 (791) 4.1–7.4	2–10%
HbA1c (glycated hemoglobin) >6.0%	7.9 (907) 6.3–9.9			
Kleihauer-Betke positive	11.9 (910) 9.8–14.2			
Hemoglobin electrophoresis abnormal	2.7 (754) 1.6–4.1			
Anti-nuclear antibodies positive	9.4 (693) 7.3–11.8			
Antibody screening positive	3.9 (917) 2.8–5.4			
HIV positive	0.3 (763) 0.03–0.9			

AC, anticardiolipin; *CI*, confidence interval; *TSH*, thyroid-stimulating hormone; *VWF*, Von Willebrand factor.

[a] Free protein S ↓ but normal total protein S.

Korteweg. Fetal death workup. Am J Obstet Gynecol 2012.

activity (4.2%), and increased levels of VWF (14.3%), compared to healthy pregnant women (in which 2.5% and 97.5% were the cutoff points for normal ranges). Overall, inherited thrombophilias in mothers with IUFD were not more prevalent than in the normal population. This was also concluded for hyperhomocysteinemia or presence of anticardiolipin antibodies. Of the 40 women unfamiliar with the antiphospholipid syndrome before the index pregnancy with either lupus anticoagulant and/or anticardiolipin antibodies in this study, the cause of death in 12 IUFDs was placental bed pathology with origin of mechanism infarction, while 23 had other causes of death and 5 an unknown cause of death.

Of the women tested for toxoplasmosis, rubella, cytomegalovirus, herpes simplex virus (TORCH), parvovirus B19, syphilis, or hepatitis B surface-antigen, 17.9% (95% CI, 15.6–20.5) had positive IgM antibody titers to one of these infectious agents or a positive hepatitis B surface-antigen (Table 2). In 1.8% of the total cohort (n = 1025) intrauterine infection was allocated as cause of death, supported by placental or autopsy findings. Of the 739 performed fetal ear/throat and 612 placental swabs, respectively, 25.3% and 22.8% were positive for ≥1 microorganism (Table 2). Of the positive fetal and placental swabs in, respectively, 74.9% and 71.4% *Escherichia coli* or group B streptococcus was detected. Of the examined placentas (n = 1011) 12.7% (95% CI, 10.7–14.9) showed histological chorioamnionitis without funisitis and only 21.9% and 25.9% of the fetal and placental swabs in these cases were positive.

As is also shown in Table 2 abnormal findings were observed in 51.5% of performed autopsies, 89.2% of placentas, 30.6% of MRI, and 7.3% of radiography. Abnormal autopsy or placental histological evaluation were defined as abnormal findings stated in the conclusion of the pathology report performed by the pathologist. Minor abnormal findings stated in the report concerning macroscopic or microscopic examination but not mentioned in the conclusion of the

TABLE 2
Abnormal viral serology tests, cultures, and other diagnostics in 1025 intrauterine fetal deaths

	% abnormal (n tested) 95% CI	
Positive viral serology	**Maternal**	**Fetal**
Toxoplasmosis IgG	23.4 (964) 20.8–26.3	9.8 (41) 2.7–23.1
Toxoplasmosis IgM	1.4 (946) 0.7–2.3	0 (42) 0–8.4
Rubella IgG	90.5 (944) 88.4–92.3	75.7 (37) 58.8–88.2
Rubella IgM	3.2 (853) 2.1–4.6	0 (37) 0–9.5
Cytomegalovirus IgG	46.8 (941) 43.5–50.0	42.5 (40) 27.0–59.1
Cytomegalovirus IgM	2.3 (964) 1.4–3.4	0 (46) 0–7.7
Herpes simplex virus IgG	63.3 (811) 59.8–66.6	50.0 (40) 33.8–66.2
Herpes simplex virus IgM	7.9 (826) 6.1–9.9	0 (41) 0–8.6
Parvovirus B19 IgG	62.8 (869) 59.5–66.1	45.0 (40) 29.3–61.5
Parvovirus B19 IgM	2.1 (892) 1.3–3.3	2.3 (43) 0.06–12.3
Syphilis	0.5 (946) 0.2–1.2	2.3 (44) 0.06–12.0
Hepatitis B surface-antigen	0.5 (934) 0.2–1.2	
Cultures		
Urinary sediment nitrite +	3.8 (771) 2.5–5.4	
Chlamydia PCR	1.6 (706) 0.8–2.8	
Group B streptococcus	17.9 (853) 15.4–20.7	
Fetal swabs	25.3 (739) 22.2–28.6	
Placental swabs	22.8 (612) 19.6–26.4	
Other diagnostics		
Autopsy	51.5 (705) 47.4–55.2	
Placental examination	89.2 (1012) 87.2–91.1	
Cytogenetic analysis	11.9 (362) 8.7–15.7	
MRI	30.6 (62) 19.6–43.7	
Radiography	7.3 (409) 5.0–10.3	

CI, confidence interval; *MRI*, magnetic resonance imaging; *PCR*, polymerase chain reaction.

Korteweg. Fetal death workup. Am J Obstet Gynecol 2012.

report were not regarded as clinically relevant. Cytogenetic analysis was performed in 700 IUFDs (68.3%) and a successful result was obtained in 362 deaths (51.7%). The prevalence of a chromosomal abnormality in these 362 IUFDs was 11.9% (95% CI, 8.7–15.7). Of these 43 chromosomal abnormalities, 37.2% was trisomy 21, 23.3% trisomy 18, 16.3% monosomy (45, X), 4.6% trisomy 13, and in 18.6% other chromosomal abnormalities were found.

Adjudication of cause of death

The main causes of death in the total cohort of 1025 deaths were placental pathology (65.2%), congenital anomaly (4.8%), infection (1.8%), and other (5.0%) while in 23.2% the cause remained unknown. Subgroups of causes, mechanism, and origin of mechanism of death are presented in Table 3. Deaths caused by fetal maternal hemorrhage (FMH) of unknown origin with evidence of fetal anemia confirmed by placental examination and/or autopsy (1.3%) were classified according to the Tulip classification as caused by placental parenchyma pathology (n = 10) or placenta not otherwise specified (n = 3), both with origin of mechanism excessive bleeding. In 10.6% of the total cohort FMH was observed as a contributing factor. Diabetes-related disease was cause of death only twice in which maternal diabetic coma resulted in fetal death. In 4.0% of 1025 deaths diabetes-related disease was a contributing factor. Maternal hyperthyroidism resulted in fetal death only once; in 2.1% thyroid-related disease was a contributing factor. Most deaths in the maternal disease group "other" (1.3%) were caused by a known antiphospholipid syndrome before the index pregnancy (0.9%). The most frequent observed maternal disease during pregnancy was hypertension-related disease (15.1%); placental bed pathology was in 65.8% the cause of these deaths.

Value of diagnostics

After the evaluation of the contribution of each test for adjudication of cause of death according to the Tulip classification, the most valuable tests were placental examination in 95.7% (95% CI, 94.2–96.8), autopsy in 72.6% (95% CI, 69.2–75.9), and cytogenetic analysis in 29.0% (95% CI, 24.4–34.0) (Table 4). The tests not mentioned in Table 4 including coagulation tests and radiography were respectively never or only once allocated as valuable for adjudication of the cause.

On the basis of our findings we derived the following flowchart for an optimal workup of basic and selective diagnostics to determine the cause of fetal death (Figure 2).

Comment

A fetal death workup guideline helps in elucidating the cause of fetal death but also aims to prevent unnecessary investigations. There is no international generally accepted diagnostic guideline for fetal death. This study primarily addressed the contribution of a uniform extensive nonselective protocol of diagnostic tests for the adjudication of the cause according to the Tulip classification in 1025 fetal deaths. This resulted in a proposal for a basic and additional workup guideline. In the cognitive process of making explicit the complex

TABLE 3
Cause of death, mechanism and origin of mechanism in 1025 IUFDs according to the Tulip classification[7]

		Mechanism of death and origin of mechanism				
Cause of death % (n)	Total	Cardiocirculatory; congenital heart malformation	Cardiocirculatory; fetal hydrops	Cardiocirculatory; supraventricular tachycardia	Cardiocirculatory; umbilical cord occlusion	Placental; abruptio placentae
Chromosomal defect; numerical	2.8 (29)	50.0 (2)	20.0 (4)			
Chromosomal defect; structural	0.1 (1)					
Congenital anomaly: syndrome; monogenic	0.1 (1)					
Congenital anomaly: syndrome; other	0.2 (2)					
Congenital anomaly: central nervous system	0.1 (1)		5.0 (1)			
Congenital anomaly: heart and circulatory system	0.4 (4)		10.0 (2)	50.0 (1)		
Congenital anomaly: digestive system	0.1 (1)					
Congenital anomaly: neoplasm	0.3 (3)		5.0 (1)			
Congenital anomaly: other; single organ	0.1 (1)					
Congenital anomaly: other; multiple organ	0.6 (6)	50.0 (2)				
Placenta: placental bed pathology	31.4 (322)					100 (61)
Placenta: placental pathology; development	18.8 (193)					
Placenta: placental pathology; parenchyma	2.8 (29)					
Placenta: placental pathology; localization	0.1 (1)					
Placenta: umbilical cord complication	5.7 (58)				98.3 (58)	
Placenta: not otherwise specified	6.4 (66)					
Infection: transplacental	1.0 (10)		20.0 (4)			
Infection: ascending	0.8 (8)				1.7 (1)	
Other: fetal hydrops of unknown origin	3.3 (34)		35.0 (7)			
Other: maternal disease; diabetus mellitus	0.2 (2)					
Other: maternal disease; hyperthyroidism	0.1 (1)			50.0 (1)		
Other: maternal disease; other	1.3 (13)					
Other: out of the ordinary	0.1 (1)					
Unknown: despite thorough investigation	15.8 (162)		5.0 (1)			
Unknown: important information missing	7.4 (76)					
Total % (n)	100 (1025)	100 (4)	100 (20)	100 (2)	100 (59)	100 (61)

IUFD, intrauterine fetal death.

Korteweg. Fetal death workup. Am J Obstet Gynecol 2012.

(continued)

chain of events eventually leading to adjudication of an underlying cause of death during our panel meetings, we also assessed risk factors and the clinical setting in which fetal death occurred.[7]

In accordance with others,[15-17] we cannot overemphasize the value of autopsy. Earlier studies also provided evidence that after IUFD routine macroscopic and histological examination of the placenta is a necessary complement to autopsy confirming clinical and/or autopsy findings.[18-20] Both tests provide information that is pertinent to nearly every potential cause of fetal death and in the majority of cases exclude causes if there are no signs. Further selective diagnostic testing may follow after pathology results and/or suspect clinical characteristics.

Although an autopsy is optimal, earlier studies have acknowledged the value of MRI as an alternative,[21] particularly for cerebral pathology.[22] Our low performance rate of MRI (6.0%) is probably due to our high autopsy rate, clinicians not being familiar with fetal MRI and unavailability of MRI services. MRI was adjudicated as valuable in only 2 cases and radiography even less. This is probably associated with inexperience of most radiologists with reviewing MRI after fetal death. MRI is generally advised if there is suspicion of cerebral congenital anomalies and radiography if there is suspicion of congenital anomalies and both in the absence of autopsy.[23]

We observed chromosomal abnormalities in 11.9% of our successfully karyotyped IUFDs (n = 362). In the

TABLE 3
Cause of death, mechanism and origin of mechanism in 1025 IUFDs according to the Tulip classification[7] *(continued)*

Placental; infarction	Placental; villus immaturity	Placental; hypoplasia	Placental; fetal thrombotic vasculopathy	Placental; massive perivillous fibrindeposition	Infection intrauterine	Other; excessive bleeding	None of the above	Unknown
0.7 (2)		6.1 (9)					3.0 (3)	3.2 (9)
								0.4 (1)
							1.0 (1)	
							1.0 (1)	0.4 (1)
							1.0 (1)	
								0.4 (1)
							2.0 (2)	
					7.1 (1)			
								1.4 (4)
95.9 (257)							4.0 (4)	
	100 (42)	93.2 (137)				15.4 (2)	11.9 (12)	
			100 (4)	100 (7)		76.9 (10)	7.9 (8)	
						7.7 (1)		
							65.3 (66)	
					42.9 (6)			
					50.0 (7)			
0.4 (1)								9.2 (26)
		0.7 (1)					1.0 (1)	
2.6 (7)							2.0 (2)	1.4 (4)
								0.4 (1)
								56.9 (161)
0.4 (1)								26.5 (75)
100 (268)	100 (42)	100 (147)	100 (4)	100 (7)	100 (14)	100 (13)	100 (101)	100 (283)

adjudication of the cause, cytogenetic analysis was the third most valuable test (29.0%) and is advised for all IUFDs by invasive testing before labor. If no parental consent for invasive testing is given, an umbilical cord sample postpartum was second best.[10] Newer cytogenetic techniques in which tissue culture is not required such as molecular karyotyping by array-based analysis results in a more precise evaluation of submicroscopic cytogenetic imbalances and should be considered when karyotyping fails.

FMH was attributed as cause if there was evidence of fetal anemia confirmed by placental examination and/or autopsy in 1.3%. Others reported 3% of deaths caused by FMH.[24] We observed FMH however in 11.9% of tested women, comparable to 8% reported in stillbirths earlier.[25] This 12% frequency may be an overestimate since many of these cases could have been related to a nonpathologic event. We would be inclined to advise investigation of FMH only in cases with suspicion. However, to preserve erythrocytes until after pathology results are available is technically impossible. We therefore recommend investigation of FMH in all fetal deaths before induction of labor, to exclude FMH caused by labor itself.

The most convincing proof of an infectious cause of death is an autopsy with evidence of organ involvement with an organism potentially able to cause stillbirth and/or histological placental examination with infectious findings.[26] Chorioamnionitis by itself (12.7%) should

TABLE 4
Valuable tests in relation to determination of cause in 1025 intrauterine fetal deaths

		Value of diagnostics								
Diagnostic tests		Kleihauer-Betke			Glucose testing			Hb electro-phoresis		
Cause of death, n	Total	Established	Excluded	Missed	Established	Excluded	Missed	Established	Excluded	Missed
Chromosomal defect; numerical	29									
Chromosomal defect, structural	1									
Congenital anomaly	19									
Placenta: placental bed pathology	322						1			
Placenta: placental pathology; development	193	1		1	2	6	1			
Placenta: placental pathology; parenchyma	29	10				1				
Placenta: placental pathology; localization	1									
Placenta: umbilical cord complication	58									
Placenta: not otherwise specified	66	2			1	1				
Infection	18					1				
Other: fetal hydrops of unknown origin	34		1						1	33
Other: maternal disease; diabetes mellitus	2				2					
Other: maternal disease; hyperthyroidism	1									
Other: maternal disease; other	13									
Other: out of the ordinary	1									
Unknown: despite thorough investigation	162		2			2				
Unknown: important information missing	76		2	1		3				
Total, n	1025	13	5	2	5	14	2	0	1	33
n tested		910			907			754		
n not tested				115			118			271
Total, % valuable		2.0		1.7	2.1		1.7	0.1		12.2

Diagnostics were adjudicated valuable if: establishing cause of death, excluding cause of death or missing for determination of cause of death if there was a suspected cause.
AB, antibodies; *MRI*, magnetic resonance imaging.

Korteweg. Fetal death workup. Am J Obstet Gynecol 2012.

(continued)

not be considered a cause of stillbirth. TORCH serology and cultures are traditionally advised in the evaluation of stillbirth. In our study placental examination and autopsy were able to support an intrauterine infection as cause in only 1.8% of all fetal deaths. This is supported by others.[16,27] More infections were reported by Petersson et al,[4] 24% in fetal deaths >22 weeks of gestation, most commonly group B streptococcus. Differences could be explained due to our strict criteria[7] and the lack of use of molecular diagnostic technology. Based on our findings we no longer recommend routine screening for infections. We advise obtaining and storing blood for maternal virus serology for all IUFDs. This can be analyzed if there are pathological infectious findings. If there is clinical suspicion of infection this should be analyzed together with maternal, fetal, and placental cultures. However, in parts of the world with a high prevalence of infectious causes such as syphilis and malaria[28] testing all deaths may well be advisable.

We recently concluded after analysis of 750 fetal deaths that, except for VWF, acquired and inherited thrombophilic defects were not associated with fetal death. Although a group of women with fetal death had lowered plasma levels of acquired thrombophilic defects when compared to healthy pregnant women, these levels remained within the normal ranges for nonpregnant women. These data provided no evidence for routine testing of inherited or acquired thrombophilic defects after fetal death.[8] This is confirmed by our data of 1025 evaluated fetal deaths. Thrombophilia testing should be considered in women with IUFD and a family history of hereditary thrombophilia or a personal history of venous thromboembolism, to prevent further maternal thromboembolisms.[29]

Overall about 10% of fetal deaths are associated with maternal disease.[30] We observed hypertension and diabetes-related disease during pregnancy in, respectively, 15.1% and 4.0% of the total cohort. Diabetes-related and thyroid-related disease as cause of death were rare. However, an increased HbA1c was often observed illustrating the needs for further scientific investigation into unestablished gestational diabetes. Testing for maternal disease in asymptomatic women has been suggested by many[6]; we recommend testing selectively if there is a suspect clinical history or suspect current pregnancy. In cases with fetal hy-

TABLE 4
Valuable tests in relation to determination of cause in 1025 intrauterine fetal deaths *(continued)*

Antibody screening			Anticardiolipin AB			Mother viral serology			Mother swabs			Fetus swabs		
Established	Excluded	Missed	Established	Excluded	Missed	Established	Excluded	Missed	Established	Excluded	Missed	Established	Excluded	Missed
			1	1			2							
							1			1			1	
							2	1						
						8			3		1	6		1
	30	4					31	3		1				1
			7											
	1						2	1		1	1		2	1
							1	2		1			1	1
0	31	4	8	1		8	39	7	3	4	2	6	4	4
917			791			964			853			739		
		108			234			61			172			286
3.4		3.7	1.1		0.0	4.9		11.5	0.8		1.2	1.4		1.4

drops tests to prove red cell alloimmunization, parvovirus B19 serology and hemoglobin electrophoresis are advised to exclude other causes of death as these were considered valuable in these cases. Obtaining amniotic fluid, which is advised for all fetal deaths, may also provide opportunities for investigation into metabolic disease.

The value of this nationwide study with 50 participating hospitals lies in its size and the approach in which fetal death was evaluated: a case-by-case evaluation of 1025 IUFDs. For establishing the cause of death we used the Tulip classification for perinatal mortality that separates cause, mechanism, and risk factors that are often mixed in other systems.[31] Having strict criteria, the Tulip classification system itself influenced our adjudication of causes and judgment as to whether tests were valuable. Not all possible tests are needed to classify cause of death in the Tulip classification. The distribution of causes of death obviously also influences the contribution of diagnostic tests.

In general, the occurrence of diagnostic test abnormalities in our study was low. A comparison of abnormal test results in IUFD vs live born was neither planned nor performed. Some abnormal tests may also be relatively common in live births and therefore it may be difficult to judge their relevance when found in a cohort of stillbirths. However in our procedure of classifying the cause, we considered all available information including the clinical setting in addition to abnormal test results and other diagnostics.

The clinical implications of our findings are presented in a flowchart for diagnostic workup to determine cause of fetal death according to the Tulip classification (Figure 2). Autopsy, placental examination and cytogenetic analysis are the basis for diagnostic workup for all fetal deaths. We recommend further individualized sequential testing to avoid unnecessary investigations and positive test results that do not identify the cause of stillbirth and bring on anxiety. Modifications to the guideline, for example testing of HbA1c, can be applied in view of risk factor assessment, declined autopsy consent, endemic differences in causes of fetal death, local preferences and different cultures, technology, or financial resources.

Participating hospitals

We thank 50 Dutch hospitals for participating in our national IUFD study: Albert

TABLE 4
Valuable tests in relation to determination of cause in 1025 intrauterine fetal deaths *(continued)*

Fetus viral serology			Cytogenetic analysis			Autopsy			Placenta			MRI		
Established	Excluded	Missed	Established	Excluded	Missed	Established	Excluded	Missed	Established	Excluded	Missed	Established	Excluded	Missed
			29			13	3	1	13	6		1		
			1											
				4	6	15	2	1	5	3				
		1		20	16		155	44	319					
	1			9	8	1	59	28	193					
				1	1	5	6	4	28					
							1		1					
					1	6	14	6	50		1	1		
		1		1	5		22	11	66					
1						15	1		18					
	2	32		15	6		26	8		34				
							1							
						1				1				
							10		8	3	1			
						1			1					
	2			24	19		139	17		153	3		1	
	2	2		1	25		16	59		66	5			
1	7	36	30	75	87	57	455	179	702	266	10	2	1	0
46			362			705			1012			62		
		979			663			320			13			963
17.4		3.7	29.0		13.1	72.6		55.9	95.7		76.9	4.8		0.0

Schweitzer Hospital, Dordrecht; Alysis Zorggroep Zevenaar; Amphia Hospital, Breda; Amstelveen Hospital; Antonius Hospital, Sneek; Atrium Medical Center, Heerlen; Bronovo Hospital, the Hague; Bethesda Hospital, Hoogeveen; Deventer Hospitals; Diaconessenhuis, Utrecht; Erasmus University Hospital Rotterdam; Flevo Hospital, Almere; Gelre Hospitals, Apeldoorn; Gelre Hospitals, Zutphen; Groene Hart Hospital, Gouda; Haga Hospital, the Hague; Isala Klinieken, Zwolle; Kennemer Gasthuis, Haarlem; Lange Land Hospital, Zoetermeer; Leids University Medical Center, Leiden; Maasland Hospital, Sittard; Martini Hospital, Groningen; Meander Medical Center, Amersfoort; Medical Center Alkmaar; Medical Center Leeuwarden; Medical Center Rijnmond Zuid, Rotterdam; Medical Spectrum Twente, Enschede; Medical Center Haaglanden, the Hague; Nij Smellinghe, Drachten; Rivierenland Hospital, Tiel; Rijnland Hospital, Leiderdorp; Rode Kruis Hospital, Beverwijk; Ruwaard van Putten Hospital, Spijkenisse; Sint Elisabeth Hospital, Tilburg; Sint Franciscus Gasthuis, Rotterdam; Sint Lucas Andreas Hospital, Amsterdam; Scheperhospital, Emmen; Slingeland Hospital, Doetinchem; Streekziekenhuis Midden Twente, Hengelo; Twee Steden Hospital, Tilburg; University Medical Center Groningen; University Medical Center Utrecht; University Medical Center Sint Radboud, Nijmegen; VieCuri Medical Center Noord Limburg, Venlo; Vlietland Hospital, Vlaardingen; Vrije University Medical Center, Amsterdam; Walcheren Hospital, Vlissingen; Westfries Gasthuis, Hoorn; Wilhelmina Hospital, Assen; Zaans Medical Center, Zaandam. ■

FIGURE 2
Guideline flowchart for diagnostic workup to investigate cause of fetal death

Basic investigation for all intrauterine fetal death antepartum
review previous obstetric history, current pregnancy, antenatal investigations, maternal and paternal family and personal history
↓
counsel parents on value autopsy, placental examination, and cytogenetic analysis
↓
before induction of labor perform invasive cytogenetic analysis (amniocentesis or chorionic villus biopsy) and preserve tissue for possible additional future tests
↓
test for fetal maternal hemorrhage
collect and store serum for maternal virus serology; analyze selectively
↓
Basic investigation for all intrauterine fetal death postpartum
↓
external fetal examination preferably by expert: documentation of morphological (ab)normalities and photo's
register birthweight and trimmed placental weight
↓
if no informed consent for invasive cytogenetic analysis, sample umbilical cord for cytogenetic analysis
↓
placental examination including histopathology
↓
if antepartum/postpartum suspected cerebral congenital anomalies → MRI
if antepartum/postpartum suspected congenital anomalies → radiography
↓
autopsy
↓
if no autopsy consent → discuss selective autopsy
external fetal examination by expert familiar with congenital anomalies including photographs, MRI, and radiography

Selective investigation intrauterine fetal death
if clinical signs and symptoms of maternal disease:
suspected hypertension-related disease → blood tests and test urine for albumen
suspected disturbed thyroid function → thyroid-stimulating hormone, free thyroxine (T4)
suspected diabetes-related disease, macrosomia (history), a strong family history of diabetes, or obesity → glucose screening: such as glycated hemoglobin (HbA1c) or oral glucose tolerance test
↓
if suspected drug use → toxicology screen
↓
if signs of fetal hydrops → antibody screening, parvovirus B19 serology and hemoglobin electrophoresis, amniotic fluid testing for possible investigation into metabolic disease
↓
if clinical signs of infection: collect and analyze vaginal-rectal swab mother, fetal, and placental swabs and analyze maternal virus serology and amniotic fluid for molecular diagnostic technology
if signs of infection in placenta or at autopsy → determine maternal viral serology and amniotic fluid for molecular diagnostic technology
↓
in women with a family history of hereditary thrombophilia or a personal history of venous thromboembolism→ perform thrombophilia work-up several months postpartum

All IUFD: multidisciplinary panel classification meetings for evaluation cause of intrauterine fetal death

IUFD, intrauterine fetal death; *MRI*, magnetic resonance imagine.

Korteweg. Fetal death workup. Am J Obstet Gynecol 2012.

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